

REMARKS

Claims

Claims 1-4, 10-19, and 23-25 are pending as shown above. Claims 10-18 and 24 are withdrawn as being drawn to non-elected inventions and claims 1-4, 19, 23, and 25 are under active consideration.

Rejections Withdrawn

The rejection of claims 1-4, 19-21, 23, and 25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Domenighini et al. (International Patent Application WO 93/13202; hereinafter "Domenighini") was withdrawn in view of the previous amendments. (Office Action, paragraph 2). In addition the previous rejection under 35 U.S.C. § 112, 1st paragraph has also been withdrawn. *Id.*

35 U.S.C. § 103

Claims 1-4, 19, 23 and 25 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Domenighini in view of Pizza et al. *Molec. Microb.* (1994) 14:51-60 (hereinafter "Pizza") and U.S. Patent No. 6,019,982; (hereinafter "Clements"). (Office Action, page 4). Domenighini was cited for teaching DNA molecules that encode mutant detoxified heat labile toxin of *E. coli* and mutant detoxified cholera toxin having mutations in the A subunit at positions 63 and 192. *Id.* Although the Office acknowledges that Domenighini fails to disclose an Arg192Gly mutations, Pizza was cited for allegedly teaching that an Arg192-Asn mutation decreases the rate of proteolysis and activation in vivo and Clements was cited for teaching the Arg192Gly mutation. *Id.*

Applicants respectfully traverse the rejection and supporting remarks.

As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ2d 1385, 1397 (2007) and Patent Office Guidelines regarding determining obviousness issued in view of *KSR*, an obviousness rejection is only proper when the proposed combination of elements results in a predictable outcome (see, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195,

October 10, 2007, emphasis added):

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one or ordinary skill in the art at the time of the invention.

Rather, the Supreme Court in *KSR* reiterated that an obviousness inquiry is fact-dependent and that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 82 USPQ2d at 1389. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

Thus, a rejection cannot be predicated on the mere identification of individual components, in this case particular single mutants, of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed subject matter, would have selected and modified these components for combination in the manner.

In the instant case, the combination of references does not teach or suggest that the claimed double mutants were predictable in terms of being detoxified and/or immunogenic.

As a threshold matter, Applicants note that none of the references actually show that the claimed double mutants are both detoxified and immunogenic, let alone show that the claimed molecules are predictable as required to show obviousness. As previously noted, Domenighini teaches that mutating the Arg192 residue does not result in reduced toxicity. See, Table I, row O of Domenighini on page 46 of the reference. Simply put, Domenighini does not teach anything predictable about double mutants generally, and teaches away from the specifically claimed detoxified double mutant.

Pizza also fails to teach anything about double mutants as claimed. Furthermore, contrary to the Examiner’s assertions, Pizza does not teach that mutating position Arg192

decreases the rate of proteolysis. Rather, like Domenighini, Pizza teaches away from mutating the Arg192 residue to reduce proteolysis and/or toxicity (see, page 57, right column of Pizza, emphasis added):

Arg-192. Arg-192 is part of the surface exposed loop ... that needs to be cleaved at the Arg residue in order to allow entrance of the A1 domain into the cell membrane and cause toxicity (Spicer and Noble, 1982). Substitution with a polar amino acid (Asn) was designed to introduce a residue still surface-exposed but resistant to proteolysis. Unexpectedly, the mutant LT was found to be fully toxic, suggest either that the substitutions did affect proteolysis at all, or that the rate of proteolysis was only decreased to a level that did not affect toxicity in vivo.

Thus, Pizza teaches nothing about double mutants and teaches away from mutating the Arg-192 residue inasmuch as the Arg192Asn mutation had no effect on toxicity.

Finally, Clements also fails to establish anything about the predictable use of double mutants, as claimed. Clements discloses one mutant only and gives no indication that double mutants would be either functional or in any way desirable. Furthermore, given that Domenighini and Pizza both clearly teach that their Arg192 mutations do not detoxify the protein, the combination of cited references does not establish predictability of this single mutant, let alone the claimed double mutants.

Therefore, the Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." In fact, the evidence is to the contrary. The cited art fails to provide evidence that a mutated CT-A or LT-A protein comprising the combined substitutions at the position corresponding to Ser-63-Lys and the position corresponding to Arg-192-Asn/Gly would not only retain immunogenicity, but also be detoxified.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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